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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,896	TAKEDA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 56-106* is/are pending in the application.

4a) Of the above claim(s) *56-62,65 and 88-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,63,64 and 66-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/2006; 7/10/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of February 8, 2008, to the Restriction Requirement dated December 12, 2007 has been entered. No claims have been amended, cancelled or newly added. Claims 1-25 and 56-106 are pending in the application.

Election/Restrictions

Applicants' election of Group I (claims 1-25, 63, 64 and 66-87), drawn to an isolated nucleic acid, a nucleic acid fragment, or a gene cassette having a nucleic acid sequence encoding a transposon, wherein the nucleic acid sequence has a methylation at at least one nucleotide; a vector and composition comprising the same; a kit, and a nucleic acid introduction system comprising said nucleic acid and a transposase, is acknowledged. Applicants' species election of sleeping beauty (SB), mouse, promoter, cellular genome, microinjection and stem cell, is further acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL. Claims 56-62, 65 and 88-106 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely responded to the restriction (election) requirement in the reply filed February 8, 2008.

Elected claims 1-25, 63, 64 and 66-87 are under current examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on August 8, 2006 and July 10, 2007 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and indicated as such on Form PTO-1449.

Objections to the Specification

The Title of the disclosure is objected to, because the title does not match the title of the Application (or that provided in the Oath and Application Data Sheet). Appropriate correction is required.

The brief description of the drawings for Figures 1, 2, 4, 5, 6 and 7 are objected to, because there are no figures present corresponding to their descriptions. For example, Figures 1A, 1B, 1C and 1D have corresponding descriptions, however, there is no Figure 1.

Figures 5A-5F have not been provided with a description. The brief description of Figure 5 fails to identify Figures 5A-5F. Appropriate corrections are required.

Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

37 CFR 1.821 (a) states: Nucleotide and/or amino acid sequences as used in §§1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. 37 CFR 1.821 (d) states: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Deleted:

Neither the sequence alignments depicted in Figures 5A-E, nor the descriptions of the drawings refer to the sequences by SEQ ID NO. As it is not clear whether the sequences of Figures 5A-E are present in the CRF listing, Applicants are required to check both the as filed paper and CRF sequence listings to ensure concordance with the sequences depicted in Figures 5A-E. The instant application may be placed in compliance with 37 CFR 1.821-1.825 by amending either the Figures or the brief description of the Figures to refer to appropriate SEQ ID NOS.

Claim Objections

Claims 3 and 15 are objected to because of the following informalities: the claims recite: "methylation is present at least C in a CG sequence". An amendment to the claim to state: "methylation is present at a C residue in a CG sequence" would be remedial.

Claim 75 is objected to because of the following informalities: the claim recites: "A nucleic acid fragment according to Claim 66, the DNA of the cell is selected from the group". It appears that the term "wherein" is missing from the claim, following the comma. Appropriate correction is required.

Claim 75 is objected to because of the following informalities: the claim recites: "therein the transposase is SB protein". A claim amendment replacing "therein" with "wherein" would be remedial.

Claim 14 is objected to because the claim refers to "said nucleic acid sequence having a methylation at at least one nucleotide". However, the claim is drawn to a vector having a nucleic acid encoding a transposon and a nucleic acid encoding a desired gene. The claim should be amended to indicate which nucleic acid sequence contains the at least one nucleotide methylation. Commensurate with the teachings of the specification, it would appear that the methylation is required in at least one nucleotide of the transposon sequence.

Claims 25, 63, 66 and 81 are similarly objected to for reasons set forth in the above indicated objection of claim 14.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66, 76, 77-79, 81 and 83 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 ¶1 "Written Description" Requirement, Rev. 1, 2008; at http://www.uspto.gov/web/menu/written.pdf.

The claims broadly embrace nucleic acids comprising portions of inverted repeat sequences set forth in SEQ ID NOS: 20 or 21, or sequences having at least 80% homology to the sequence set forth in SEQ ID NO: 26 (a portion of a repeat sequence), having the capability of binding a transposase and incorporate into a DNA in a cell; wherein the transposase has at least 80% amino acid homology to the sequence set forth in SEQ ID NO: 3 or is a variant of SEQ ID NO: 3, or a variant of the sequence set forth in SEQ ID NO: 2, encoding a transposase. As the variants of the inverted repeats retain the ability to bind a transposase and integrate into cellular DNA, and the variants of the transposase need to maintain enzymatic function, the claims require the variant sequence structures to retain function, necessitating structure/function relationships.

The specification discloses the sequence encoding the inverted repeats and direct repeats of the SB transposon as SEQ ID NOS: 20, 21 and 26, and the nucleotide and polypeptide sequences of the SB transposase as SEQ ID NOS: 2 and 3, respectively, and previously reported in the prior art. The specification further exemplifies transposition of nucleic acids harboring the SB direct repeat sequences, catalyzed by the SB transposase.

However, the specification is silent on any structure/function relationship for the numerous variants of SEQ ID NOS: 20, 21 and 26, that share 80% sequence homology or contain portions of the direct repeat, that retain the ability to bind SB transposase and integrate into cellular DNA. The specification is further silent on the numerous variants of SEQ ID NOS: 2 and 3 that retain transposase activity. The numerous sequence variants having transposon and transposase activity, were not known at the time of the instant invention by Applicants, and include sequences yet to be discovered.

The SB inverted repeat variants and the transposase variants thus constitute a genus of sequences that encompasses other nucleic acids and protein sequences and their variants yet to be discovered and analyzed for their ability to display biological activities for transposition functional activity. Moreover, the numerous variant sequences, are not completely described in

the prior art or the present specification. As the specification fails to describe other members of the genus by complete or partial structure, having the ability to bind transposase, integrate into cellular genome or retain transposase activity, the disclosed species are not representative of the numerous variants encompassed by the claims.

As the specification only discloses the species of SB inverted repeats and their cognate transposase, disclosed as SEQ ID NOS: 20, 21, 26, 2 and 3, that display transposition promoting activity, the species do not constitute a substantial portion of the claimed genus.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

As stated in MPEP 2163 II: If the application as filed does not disclose the complete structure (or acts of a process) of the claimed invention as a whole, determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The instant specification is devoid of a description for the numerous variant nucleotide and protein sequences that retain specific biological activities with respect to transposition. The specification merely discloses the inverted repeat species of SEQ ID NOS: 20, 21, 26, and the single transposase of SEQ ID NOS: 2 and 3. No other variants of these sequences displaying the requisite biological activities are described. Thus, Applicants have failed to demonstrate possession of the numerous nucleotides and proteins claimed. Disclosure of function alone is little more than a wish for possession; it does not satisfy the written

description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate").

The disclosed structural features of SEQ ID NOS: 20, 21, 26, 2 and 3, do not constitute an adequate description to demonstrate possession of the numerous nucleic acid and polypeptide sequences claimed. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11).

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicants have not described the numerous nucleic acid and protein sequences that retain the requisite biological activities. As such, the Artisan of skill could not predict that Applicant possessed any additional species, except for that of SEQ ID NOS: 20, 21, 26, 2 and 3.

Therefore, the breadth of the claims as reading on numerous variant inverted repeat and transposase sequences that retain the required biological activities, including sequences yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, and the limited information provided in the specification, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of numerous variant transposon and

transposase sequences at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66, 76, 77-79, 81 and 83 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a nucleic acid fragment comprising SB transposon inverted repeat sequences set forth as SEQ ID NOS: 20, or 21 or 26, having the capability of binding their cognate transposase (said transposase encoded by SEQ ID NOS: 2 and 3), and incorporating into a DNA in a cell, does not reasonably provide an enablement for a portions or variants of the inverted repeat sequences to recognize and bind SB transposase variants and incorporate into the DNA of a cell, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on issues related to the absence of an enabling disclosure for the ability to use sequence variants of SB transposon inverted repeats, and sequence variants of the SB transposase to incorporate transgenes into the chromosomal DNA of a cell. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The claims broadly encompass nucleic acids comprising portions of inverted repeat sequences set forth in SEQ ID NOS: 20 or 21, or sequences having at least 80% homology to the sequence set forth in SEQ ID NO: 26 (a portion of a repeat sequence), having the capability of binding a transposase and incorporate into a DNA in a cell; wherein the transposase has at least 80% amino acid homology to the sequence set forth in SEQ ID NO: 3 or is a variant of SEQ ID NO: 3, or a polynucleotide variant of the sequence set forth in SEQ ID NO: 2, encoding a transposase. As the variants of the inverted repeats retain the ability to bind a transposase and integrate into cellular DNA, and the variants of the transposase need to maintain enzymatic function, the claims must be enabling for the various variant sequence structures to retain function, for use in vectors for introduction of transgenes into cellular DNA of the cell, that in turn undergo transposition.

As a first issue, the instant specification, while teaching the left and right inverted repeat IR/DR sequences of the SB transposon (set forth as SEQ ID NOS: 20, or 21 or 26), with one sequence representing a transposon family consensus repeat sequence, fails to provide any information regarding the numerous variants of the SB transposon repeats that retain biological function. The specification is silent on any structure/function relationship for the numerous variants of SEQ ID NOS: 20, 21 and 26, that share 80% sequence homology or contain portions of the direct repeat, that retain the ability to bind SB transposase and integrate into cellular DNA. As the prior art is further silent on the variants of SB transposon IR/DR sequences, a person of skill in the art would need to engage in further experimentation to discover and characterize the the variant sequences that retain transposition function. Such experimentation thus constituting an undue burden on the skilled artisan.

As a second issue, the instant specification fails to describe SB transposase variants having at least 80% amino acid homology to the sequence set forth in SEQ ID NO: 3 or other variants of SEQ ID NO: 3, or the numerous variants of the polynucleotide sequence set forth in SEQ ID NO: 2, encoding a transposase that retain transposase activity. The numerous sequence

variants having transposon and transposase activity, were not known at the time of the instant invention by Applicants and are therefore not representative of the numerous variants encompassed by the claims. The prior art at the time of filing did not teach the large number of possible sequence variants of SEQ ID NOS: 2 and 3 that retain biological activities substantially the same nature as that of the SB transposase.

With regard to changes in the nucleotide sequences in the IR/DR region of the transposon, it should be noted that even a single nucleotide alteration could result in alteration or loss of function. Kimchi-Sarfaty et al. (Science 315:526-528; 2007) have recently reported that a single silent nucleotide polymorphism is sufficient to change substrate specificity, altering substrate inhibitor interactions (Title and Abstract). The mechanism by which said substrate specificity is changed remains unknown.

With regard to variants of SEQ ID NOS : 2 and 3, altering the SB transposase sequence, the prior art of Bowie, et al. (Science, 247: 1306-10, 1990) provide notable insight into the lack of reasonable predictability for the mutation of any particular protein. Specifically, Bowie et al. explain that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). Bowie continues: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10). These observations have been further supported by the findings of Skolnick et al. (TIBTECH 18:34-39, 2000), stating: "Knowing a protein's structure does not necessarily tell you its function" (Box 2, p. 36), noting that "alternatives are needed to assign the biochemical function of the 30-50% of proteins whose function cannot be assigned by any current methods" (second column, p. 37).

Hence, the nature of the invention is not reasonably predictable for any of the various possible sequence variants of the transposon, or transposase, and their encoded proteins claimed, due to the unpredictability of structure-function relationships. Moreover, given the lack of

reasonable predictability between structure and function, the identification and subsequent analysis for biological activity of each variant protein would require further and undue experimentation.

Please note "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Given the foregoing issues, the nature of the invention is not reasonably predictable for the claimed sequence variants of SEQ ID NOS: 2, 3, 20, 21 and 26, and would require further and undue experimentation.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the person skilled in the art would be able to practice the invention as claimed by Applicants, without undue burden being imposed on such person of skill. This burden has not been met because it would require undue experimentation to demonstrate the ability to alter the sequences of the SB direct repeats and the SB transposase while retaining functional transposition.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely sets forth the nucleotide sequences of SB terminal repeats and a portion thereof, and the nucleotide sequence encoding amino acid sequence of SB transposase.

Therefore, in view of the art recognized high level of unpredictability regarding establishment of protein structure/function relationships, and the lack of knowledge regarding the specific SB IR/DR nucleotide sequences required for proper SB transposase recognition for biological function, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding the same, it is the position of the examiner that it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

To the extent that the instant claims are enabled, the following rejections over the prior art are applicable.

Claims 1-25, 63, 64, 66-75, 77, 81, 82 and 84-87 are rejected under 35 U.S.C. §103(a) as being unpatentable over Horie et al. (Proc. Natl. Acad. Sci. 98(16):9191-9196; 2001; of record), in view of Ros et al. (Genetics 157:1723-1733; April 2001; of record).

The instant claims encompass an isolated nucleic acid, a vector, a fragment and a nucleic acid introduction system, each having a nucleic acid encoding an SB transposon that has a methylation at at least one C residue in a CG sequence, further comprising a nucleic acid encoding a desired gene operably linked to said transposon, for introducing said foreign gene in a mouse. The claims are further directed to a kit comprising said nucleic acid molecule and a transposase.

Horie et al. describe the chromosomal transposition of a Tc1/mariner DNA type transposon, sleeping beauty in mice, for germ-line mutagenesis and phenotype-driven genetic screening (Title and Abstract). Specifically, Horie et al. describe the construction of a variety of plasmid expression vectors and DNA fragments comprising a 383 bp right and a 363 bp left inverted repeat/direct repeat (IR/DR) fragments of the SB transposon flanking exon 2 and intron 2 of a Piga gene together with a EGFP reporter gene inserted between the IR/DR sequences, and

under the control of the CAG promoter (constituting a portion and a desired gene, and a gene cassette; limitation of claims 1, 2 4-11, 13, 14, 16-23, 66-70, 85 and 86). The construct is further described as injected into fertilized eggs of mice to generate transgenic mouse (p. 9191, first and second columns; limitation of claims 71-74 and 87). The authors further state, to mediate transposition, another transgenic line expressing the SB transposase (SB mice, Fig. 1B) was established and mated with the line carrying the SB transposon and transgene to generate doubly transgenic mice carrying both the SB transposon and transposase (p. 9192, second column; limitation of claims 12, 24 25, 77and 82). Transposition events by cut and paste excision in the mouse cellular genome is described in Figs. 2 and 3, and first and second columns, p. 9193 (limitation of claims 75 and 84).

Regarding the kit comprising instructions and the introduction system of claims 63, 64 and 81, it should be noted that such limitations are not afforded patentable weight, as the critical limitations are the components comprising the kit and introduction system. However, the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit. See *In re Ngai*, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004) (holding that an inventor could not patent known kits by simply attaching new set of instructions to that product).

While Horie et al do not describe the transposon nucleic acid sequences as having a methylation at at least one nucleotide, the introduction of methylation into transposon sequences was known in the prior art.

Ros et al. describe the regulation of the maize transposable elements Ac/Ds by DNA methylation. (Title and Abstract). Specifically teaching that Ds elements that are hemi-methylated on one DNA strand transpose in the absence of replication (first column, p. 1724), and that the methylation on the top strand of the Ds element inverted repeat efficiently binds to transposase resulting in a hyperactive Ds element (first column, p. 1732). Ros et al. additionally describe an assay wherein a hemi-methylated daughter element is 6.3 fold more active than the other in petunia and efficiently binds the transposase protein (first column, p. 1732). The enzymatic methylation of plasmids carrying transposons, to covert cytosine residues in CpG motifs to ^{5m}C, is described in the first column, p. 1728; limitation of claims 1, 3 and 15). The

teachings of Ros et al. thus cure the deficiency of cytosine methylation of transposon sequences in Horie et al., and provide the motivation to introduce methyl C alterations into transposon coding sequences.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Horie et al. and Ros et al. to methylate at least one C residue in a CpG motif of a sequence of a transposon, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce methyl C modifications in the sequence of constructs carrying transposon sequences as taught by Ros et al., because such modifications would increase transposition frequency.

Claims 66, 76, 77-81 and 83 are rejected under 35 U.S.C. §103(a) as being unpatentable over Horie et al. (Proc. Natl. Acad. Sci. 98(16):9191-9196; 2001), in view of Ros et al. (Genetics 157:1723-1733; April 2001), as applied to claims 1-25, 63, 64, 66-75, 77, 81, 82 and 84-87 above, and further in view of Hackett et al., U.S. Patent No.: 6,489,458; effective filing date: Mar. 11, 1998).

The claims encompass, a nucleic acid fragment and a nucleic acid introduction system, each having the IR/DR repeat sequences of an SB transposon (comprising SEQ ID NOS: 20 or 21, and any of SEQ ID NOS: 22-26); having a methylation at at least one C residue in a CG sequence, further comprising a nucleic acid located between two inverted repeats, and an SB transposase having the amino acid sequence set forth in SEQ ID NO: 3, or a nucleic acid encoding a transposase, set forth in SEQ ID NO: 2.

Horie et al. describe the chromosomal transposition of a Tc1/mariner DNA type transposon, sleeping beauty in mice, for germ-line mutagenesis and phenotype-driven genetic screening (Title and Abstract). Specifically, Horie et al. describe the construction of a variety of plasmid expression vectors and DNA fragments comprising a 383 bp right and a 363 bp left inverted repeat/direct repeat (IR/DR) fragments of the SB transposon flanking exon 2 and intron 2 of a Piga gene together with a EGFP reporter gene inserted between the IR/DR sequences. The authors further state, to mediate transposition, another transgenic line expressing the SB

transposase (SB mice, Fig. 1B) was established and mated with the line carrying the SB transposon and transgene to generate doubly transgenic mice carrying both the SB transposon and transposase (p. 9192, second column).

Ros et al. describe the regulation of the maize transposable elements Ac/Ds by DNA methylation. (Title and Abstract). Specifically teaching that Ds elements that are hemi-methylated on one DNA strand transpose in the absence of replication (first column, p. 1724), and that the methylation on the top strand of the Ds element inverted repeat efficiently binds to transposase resulting in a hyperactive Ds element (first column, p. 1732).

Horie et al. and Ros et al. do not describe nucleic acid fragments having homology to portions of the SB transposon IR/DR sequences SEQ ID NOS: 20 or 21, and 80% homology to SEQ ID NO: 26, or the SB transposase nucleotide and protein sequence variants of SEQ ID NOS: 2 and 3, respectively. However, the SB transposon, its cognate transposase and their sequence structures that included the IR/DR repeats were known in the prior art.

Hackett et al. describe the SB transposase as a system for introducing nucleic acid into the DNA of a cell (Title and Abstract). Hackett et al. disclose the amino acid sequence of the SB transposase protein as SEQ ID NO: 1, the nucleic acid encoding the SB transposase protein as SEQ ID NO: 3, and the inverted repeat sequences, including their consensus sequence, as SEQ ID NOS: 4-10 (with SEQ ID NO: 6 corresponding to the instantly claimed sequence set forth as SEQ ID NO: 22, limitation of claim 80, and SEQ ID NO: 10 corresponding to the instantly claimed sequence set forth as SEQ ID NO: 26; limitation of claim 79), thus curing the deficiencies of inverted repeat and transposase sequences in Horie et al. and Ros et al.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Horie et al. and Ros et al. to methylate at least one C residue in a CpG motif of a sequence of a transposon disclosed by Hackett et al., as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce methyl C modifications in the sequences of inverted repeats disclosed by Hackett et al. having the ability to bind the SB transposase

sequences additionally disclosed, because such modifications would increase transposition frequency.

Conclusion

Claims 1-25, 63, 64 and 66-87 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Fereydoun G Sajjadi/

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633